38-78 have been added. Support for the new claims can be found at the very least in the originally filed claims, throughout the specification and in Example 6 (claims 61 and 77). Accordingly, no new matter has been added.

I. Double Patenting

Claims 1-9, 23 and 24 have been provisionally rejected under the judicially created doctrine of obviousness type double patenting as allegedly being unpatentable over claims 10, 11 and 23-31 of copending Application Serial No. 09/506,942. While acknowledging that the claims are not identical, the Examiner has stated that the claims are not patentably distinct from each other because the polypeptides in the present application are identical to the polypeptides in the divisional application for the prevention or treatment of a papillomavirus infection. Applicants respectfully traverse this rejection.

Applicants request that this provisional rejection be withdrawn due to the fact that the claims of the present application are directed to a "subunit" pharmaceutical composition essentially containing the specified papillomavirus polypeptide and, optionally, immunostimulatory polypeptides, whereas the claims of Application Serial No. 09/506,942 recite a pharmaceutical composition essentially containing a recombinant DNA vector for the expression of the specified papillomavirus polypeptide and, optionally, immunostimulatory polypeptides.

Therefore, the composition of the present invention, which is based on polypeptides, is patentably distinct from a composition based on recombinant DNA vectors as claimed in the co-pending patent Application Serial No. 09/506,942.

Accordingly, Applicants respectfully request withdrawal of the provisional rejection of claims 1-9, 23 and 24 under the judicially created doctrine of obviousness type double patenting.

II. Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-9, 21 and 32-37 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse this rejection.

Claims 1-4, 8 and 32 are allegedly indefinite for reciting the term "region." The Examiner has stated that the specification does not set forth clear metes and bounds of the intended early and late "regions" of the papillomavirus. This portion of the rejection is rendered moot in light of the cancellation of claims 1-9, 21, 23, 24 and 32-37. However, to the extent that this rejection may apply to claims 38-78, it is respectfully traversed.

Applicants submit that this term is defined in the introduction of the present application. Page 1, lines 14-18, of the specification clearly states that the HPV genome "comprises an early region and a late region. The late region contains two reading frames

L1 and L2 which code for the major components of the capsid. The early region contains at least the reading frames E1, E2, E4, E5, E6 and E7."

Moreover, the term "region" is routinely used and perfectly understood by the skilled artisan in the papillomavirus related art (see for example. page 860, first paragraph of the background chapter of Hines et al. cited by the Examiner).

Claims 2-4, 6-8 are allegedly indefinite for reciting "derived." The Examiner is not clear as to what the term "derived" means. This portion of the rejection is rendered moot in light of the cancellation of claims 1-9, 21, 23, 24 and 32-37. However, to the extent that this rejection may apply to claims 38-78, it is respectfully traversed.

New claims 39, 48 and 64; 41, 50 and 66; 52 and 68; 53 and 69; and 54 and 70, which correspond to canceled claims 2, 4 and 6-8, respectively, do not recite the term "derived."

Claims 5 and 9 are allegedly indefinite for not reciting a proper Markush group. This portion of the rejection is rendered moot in light of the cancellation of claims 1-9, 21, 23, 24 and 32-37. However, to the extent that this rejection may apply to claims 38-78, it is respectfully traversed.

New claims 51 and 67 correspond to canceled claim 5, and new claims 43, 58 and 74 correspond to canceled claim 9. These new claims recite proper Markush language.

Claim 21 is allegedly indefinite because the Examiner is not clear as to the meaning of "its" in the phrase "a pharmaceutically acceptable carrier allowing its administration by injection." This portion of the rejection is rendered moot in light of the cancellation of

claims 1-9, 21, 23, 24 and 32-37. However, to the extent that this rejection may apply to claims 38-78, it is respectfully traversed. New claims 44, 59 and 75, which correspond to canceled claim 21, do not recite the term "its."

Claims 32-37 are allegedly indefinite for reciting the term "variant." Specifically, the Examiner is not clear as to what the term means. This portion of the rejection is rendered moot in light of the cancellation of claims 1-9, 21, 23, 24 and 32-37. However, to the extent that this rejection may apply to claims 38-78, it is respectfully traversed.

New claims 71, 55, 72, 73, 56 and 57 correspond to canceled claims 32-37, respectively. Applicants submit that the meaning of the term "variant" can be found on page 4, line 37 to page 5, line 6 of the specification and refers to E6 and/or E7 non-oncogenic variant(s) mutated at the level of the residues involved in the process of transformation of the infected cell. To overcome this rejection, Applicants have introduced this limitation into new claims 71 (canceled claim 32) and 55 (canceled claim 33). Support for this amendment can be found on page 4, line 39 to page 5, line 2 of the specification. Canceled claims 34-37 have been rewritten (new claims 72, 73, 56 and 57) to recite that the nononcogenic variant of the E6/E7 is a variant of the native HPV-16 E6/E7 protein having the specified amino acids deleted as compared to the native E6 protein.

Therefore, Applicants respectfully request withdrawal of the rejection of claims 1-9, 21 and 32-37 under 35 U.S.C. § 112, second paragraph.

III. Rejections under 35 U.S.C. § 112, first paragraph

Claims 2-4, 6-8 and 32-37 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner has stated that the specification does not teach structural elements of the derivations or variants of the claims and that the specification reduces to practice only one species with the genus. Further, the Examiner has stated that since the genus embraces a wide variety of possible derivatives and variants of each polypeptide protein, the single species of each polypeptide or protein is not seen as representative for the full genus claimed. This rejection is rendered moot in light of the cancellation of claims 1-9, 21, 23, 24 and 32-37. However, to the extent that this rejection may apply to claims 38-78, it is respectfully traversed.

The above-proposed amendments in response to the rejections under 35 U.S.C. § 112, second paragraph, specify the structural elements of the claimed derived polypeptides and variants. Claims 2-4 (new claims 39, 48 and 64; 40, 49 and 65; and 41, 50 and 66, respectively) are now limited to the use of a papillomavirus polypeptide having a degree of similarity greater than 75% with the sequence of the native papillomavirus polypeptide. Claims 6-8 (new claims 52 and 68; 53 and 69; and 54 and 70, respectively) are now limited to the use of interleukin-2 and/or the co-adhesion molecule B7.1 as a polypeptide having an immunostimulatory activity. Claims 32-33 (new claims 71 and 55, respectively) are now

limited to the use of non-oncogenic E6 and/or E7 variants mutated at the level of the residues involved in the process of cellular transformation. Finally, claims 34-37 (new claims 72, 73, 56 and 57, respectively) are directed to the use of the nononcogenic E6 and E7 variants obtained from the native HPV-16 E6 and E7 proteins by deletion of the specified amino acids as compared to the native E6 and E7 proteins. Therefore, the proposed new claims as written should overcome this rejection.

Accordingly, Applicants respectfully request withdrawal of the rejection of claims 2-4, 6-8 and 32-37 under 35 U.S.C. § 112, second paragraph.

IV. Rejections under 35 U.S.C. § 102(b)

Claims 1-5, 8, 9, 21, 23 and 24 have been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Stanely et al. in WO 96/29091. This rejection is rendered moot in light of the cancellation of claims 1-9, 21, 23, 24 and 32-37. However, to the extent that this rejection may apply to claims 38-78, it is respectfully traversed.

It is well settled law that to anticipate a claim, a single reference must teach each and every element of the claim, and the single reference must be enabling. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.,* 802F.2d 1367, 1379, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986); *Atlas Powder Co. v. E.I du Pont De Nemours & Co.*, 750 F.2d 1569, 1574, 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984).

The teachings of Stanley et al. are limited to the fact that IL-12 p40 is expressed in 100% of regressing HPV-induced lesions analyzed in this study. The authors studied the

transcription of a series of cytokines including IL-2 in cervical tissues obtained from normal women (Table e) or from HPV-infected patients with either regressing (Table d) or non regressing (Tables a, b and c) lesions. From the experimental data summarized in Tables a-e, it can be concluded that all normal tissues do not express IL-12 p40 (Table e) as well as the majority of non-regressing lesions (Tables a and b), whereas IL-12 p40 expression was observed in all regressing tumors (Table d). The appearance of IL-12 p40 transcripts in the non-regressing lesions grouped in Table c was believed to indicate a possibility that the patients from whom these samples were taken were in the very early stage of regression but at a time when clinical improvement was not yet measurable (page 19, lines 1-4).

On this basis, Stanley et al. proposes the administration of IL-12 to enhance the immune response against a papillomavirus infection, eventually in the presence of one or more papillomavirus polypeptides (page 4, lines 33-37) or vector(s) expressing one or more papillomavirus polypeptides (page 5, lines 2-8).

With respect to IL-2 expression, normal cervix showed transcripts for IL-2 (Table e), as well as the majority of the regressing genital lesions (4 of 5 in Table d). IL-2 expression is also observed in some of the non-regressing lesions (5 of 8 in Table c, 2 of 7 in Table b and 0 of 8 in Table a). Thus, the pattern of IL-2 expression is quite different from the pattern observed for IL-12 p40 in the different categories of cervical biopsies analyzed in this study.

Applicants note that no cytokine shows a similar expression pattern as the one obtained for IL-12 p40 (specifically expressed in the regressing lesions and absent in normal tissues and non-regressing lesions). Therefore, the teaching of Stanely et al. could not be broadened to encompass the use of non-IL-12 immunostimulatory molecules such as IL-2 and B7.1. However, in order to expedite prosecution and not acquiesce to the Examiner's rejection, Applicants have not included the IL-12 limitation in new claims 38-78.

Therefore, Applicants respectfully request withdrawal of the rejection of claims 1-5, 8, 9, 21, 23 and 24 under 35 U.S.C. § 102(b).

V. Rejections under 35 U.S.C. § 103(a)

Claims 1-9, 21, 23, 24, 32 and 33 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Galloway, Hines et al., and Gajewski. This rejection is rendered moot in light of the cancellation of claims 1-9, 21, 23, 24 and 32-37. However, to the extent that this rejection may apply to claims 38-78, it is respectfully traversed.

In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. The Examiner can satisfy this burden by showing, first, that the cited prior art coupled with the general knowledge at the time of the invention must contain some suggestion or incentive to motivate a skilled artisan to modify or combine references. *See In re Fine,* 837 F.2d 1071,

1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988); *In re Skinner*, 2 U.S.P.Q.2d 1788, 1790 (Bd. Pat. App. & Int. 1986).

Second, the Examiner must show that the modification or combination of prior art references must have a reasonable expectation of success (at the time of the invention). *See Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991).

Lastly, the Examiner must show that the cited or combined references teach each and every limitation of the claims. *See In re Zurko,* 111 F.3d 887, 888-89, 42 U.S.P.Q.2d 1476, 1478 (Fed. Cir. 1997); *In re Wilson,* 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970).

Galloway discloses that "it should be feasible to develop prophylactic vaccines to prevent HPV infection using the L1 and L2 capsid proteins or therapeutic vaccines to modulate the development or recurrence of disease based on the E6 and E7 oncoproteins or other viral proteins." (See the abstract p 187).

Applicants draw to the Examiner's attention that such a teaching is summarized in the present application (see page 2, lines 20-27 of the specification), although based on other prior art documents (EP462187 for the prophylactic approach and WO93/02184 for the therapeutic approach).

The examiner cites Galloway's indication that most individuals have antibodies that recognize the capsid proteins, especially L2. Applicants note that the prevalence of antibodies against some HPV proteins is not representative of the disease state as explained

later in Galloway: "[s]everal groups have demonstrated that the prevalence of antibodies to the HPV 16 or 18 E7 protein is increased in cases with cervical cancer compared with age-matched controls" (see page 189 first paragraph, second column) and "it has been shown that infected individuals have type-specific antibodies to a conformational epitope(s) on the L1 protein and that these antibodies correlate strongly with a history of disease." (see page 189 second paragraph, second column). Thus, the fact that HPV proteins induce a humoral (antibody-based) immune response in patients does not correlate with a protective antitumoral effect.

Further, as noted by the Examiner, Galloway reviews the experimental assays performed in animal models with papillomavirus polypeptides. On one hand, the publication discusses prophylactic vaccinations relying on late papillomavirus polypeptides (page 190 second column) and, on the other hand, the publication discusses therapeutic vaccinations relying on early polypeptides (page 191, first paragraph, first column).

The only prior art vaccine that combines an early and a late polypeptide comprising both L2 and E7 fusion polypeptides was reported to reduce the number, severity and duration of lesions (bottom of page 190, second column and top of page 191, first column).

This L2+E7 containing vaccine is detailed in WO93/00436 (Jarrett et al.) and WO94/23037 (Campo et al.) cited in the International Search Report and in the Information Disclosure Statement annexed to the first Official Action mailed on April 8, 1999. The L2 and E7 polypeptides of BPV-4 are produced by recombinant route in E. Coli as GST fusion proteins. An antitumoral protection of immunoprophylactic type is observed in calves

vaccinated with the mixture of purified GST-fused L2 + E7 polypeptides before the viral challenge (Figure 4 and Example 2 of WO 93/00436; Experiment #4 of Table 2, page 21 and Figure 3B of WO 94/23037). When comparing Figures 3 and 4 of WO 93/00436 and Figures 3B and 3C of WO 94/23037, one concludes that vaccination with either L2 or L2 +E7 results in the same prophylactic protective effect (in other words E7 is inefficient in this context). Moreover, in spite of the presence of E7 early polypeptide, the L2+E7 vaccine does not confer any protection against tumors pre-existing before the vaccination (therapeutic effect), as indicated in WO 93/00436 (page 15, last paragraph) and in WO 94/23037 (page 21, lines 22-25).

In fact, it is interesting to note that recent data report the inefficiency of this L2+E7 formulation (Cantab Pharmaceutical's TH-GW human papillomavirus vaccine comprising a mixture of L2 and E7 polypeptides of HPV-6 produced in E. coli) and indicate that human clinical assays using the Cantab vaccine have been stopped due to its failure to demonstrate any therapeutic improvement over a placebo (see *Antiviral Agents Bulletin*, Vol. 13, enclosed herewith), thus teaching away from the claimed invention.

Furthermore, Applicants submit that none of the previously cited documents (Galloway, WO 93/00436 and WO 94/23037) mention or suggest to combine with the papilloma polypeptides an immunostimulatory molecule to enhance the protective effect of the former.

Hines et al. reports that the injection of E7-derived peptides into mice protected the mice from tumor formation after challenge with HPV-transferred tumor cells. Hines et al.

proposed a "cellular adoptive protocol" to accelerate anti-tumoral responses. This protocol involves the ex vivo stimulation of peripheral blood lymphocytes obtained from a cancer patient with HPV oncoprotein peptides (to render the patient's lymphocytes responsive to HPV), in the presence of IL-2. Applicants draw the Examiner's attention to the fact that IL-2 is necessary to lymphocyte activation into cytotoxic T Lymphocytes (as described in *Immunology*, page 281, enclosed herewith). Thus, IL-2 is not used to enhance anti-HPV immunity but to provide activation of naive lymphocytes and to make them acquire a cytotoxic phenotype. Hines et al. also reported immunoprophylactic data obtained with VLPs.

Hines et al. does not teach a vaccine combining early and late papillomavirus polypeptides as claimed in the present invention and do not teach any association with an immunostimulatory molecule to enhance immunity against papillomavirus polypeptides.

Gajewski teaches the function of B7.1 as a cofactor for in vivo IL-2 synthesis and proposes the use of B7.1 to direct the production of IL-2 necessary for the proliferation and activation of lymphocytes into cytotoxic T lymphocytes.

All together, the prior art documents disclose:

1. A composition based on one or more early papilloma polypeptides (Galloway and Hines et al.)
2. A composition based on one or more late papilloma polypeptides or VLPs (Galloway and Hines et al.)

3. A composition based on the late L2 papilloma polypeptide and the early E7 papilloma polypeptide (Galloway, WO 93/00436 and WO 94/231037).

Therefore, the state of the art discloses either antitumoral compositions relying on early papillomavirus polypeptides (composition 1) or on late papillomavirus polypeptides (composition 2) and does not motivate one skilled in the art to combine both types of polypeptides. Only prior art composition 3 associates an early (E7) and a late (L2) papillomavirus polypeptide, as claimed in pending independent claim 1 (new claims 38 and 63).

With respect to the presence of an immunostimulatory molecule, none of the cited document teach the action of said molecule to enhance the protective effect conferred by the papilloma polypeptides. Hines et al. and Gajewski disclose that IL-2 or its cofactor B7.1 can be used to induce the proliferation of naive lymphocytes obtained from a patient and to activate their cytotoxic phenotype.

Therefore, Applicants respectfully request withdrawal of the rejection of claims 1-9, 21, 23, 24, 32 and 33 under 35 U.S.C. § 103(a).

Claims 34-37 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Stanley et al., Galloway, Hines et al., and Gajewski as applied to claims 1-9, 21, 23, 24, 32 and 33 above, and further in view of Munger et al. and Crook et al. This rejection is rendered moot in light of the cancellation of claims 1-9, 21, 23, 24 and 32-37. However, to the extent that this rejection may apply to claims 38-78, it is respectfully traversed.

The discussion regarding Stanley et al., Galloway, Hines et al., and Gajewski above are incorporated herein by reference. With regard to Munger et al. and Crook et al., page 5, lines 2-6, of the present application states that Munger et al. and Crook et al. disclose the nononcogenic variants of the E6 and E7 HPV polypeptides.

As already discussed above, the combination of Stanley et al., Galloway, Hines et al., and Gajewski do not render the claimed invention obvious. Munger et al. and Crook et al. in combination with the with Stanley et al., Galloway, Hines et al., and Gajewski also do not render the claimed invention obvious.

As the specific combinations claimed in the pending independent claim 1 (new claims 38 and 63) are patentable, the patentability also applies to the dependent claims reciting a composition comprising the nononcogenic variants of the E6 and E7 HPV polypeptides.

Therefore, Applicants respectfully request withdrawal of the rejection of claims 34-37 under 35 U.S.C. § 103(a).

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned agent concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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